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EXAMINER	
ZEMAN, M	
ART UNIT	**PAPER NUMBER**
1643	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/977,787	Applicant(s) MIZZEN ET AL.	
	Examiner Mary K Zeman	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)[·] Responsive to communication(s) filed on *28 July 1999* .

2a)[ ] This action is **FINAL**. 2b)[×] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *1-5,13-41 and 43-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *1-5,13-41 and 43-49* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)[ ] All b)[ ] Some * c)[ ] None of the CERTIFIED copies of the priority documents have been:

1.[ ] received.

2.[ ] received in Application No. (Series Code / Serial Number) _____ .

3.[ ] received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) [·] Notice of References Cited (PTO-892)
15) [·] Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) [·] Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7* .
17) [ ] Interview Summary (PTO-413) Paper No(s). _____
18) [ ] Notice of Informal Patent Application (PTO-152)
19) [ ] Other:

DETAILED ACTION

Claims 1-5, 13-41 and 43-48 are pending in this application.

Applicant's election without traverse of Group I in Paper No. 14 is acknowledged. Paper No. 14 also canceled claims 6-12, 42 and 49-52.

Priority

This application is a continuation-in-part of application 08/756,621, filed 11/26/96.

Drawings

Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 48-52 been renumbered 48-53. Two claim 48's were presented.

Claim Rejections - 35 USC § 112

Claims 1-5, 13-41 and 43-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim terminology "sequence sufficiently homologous" in claims 1, 2, 13, 14, 18, 19, 23, 24, 29, 33 and 37 is vague and indefinite in that the metes and bounds of such language have not been defined. What does Applicant intend by "sufficiently homologous"? Does Applicant intend for a percent identity? Applicant's definition of a stress protein at pages 28-29 does not overcome this rejection, as it fails to particularly point out what makes a protein sufficiently homologous to a stress protein such that it would be operable in the invention as claimed..

The claim terminology "hsp65" and "hsp71" should not be abbreviated at their first appearance in a claim. The terms should be completely spelled out in their first appearance in the claims.

The metes and bounds of the term "joined with" in claim 32 are unclear. What is this "joining" is it covalent, non-covalent, a complex, a fusion? The claim will be interpreted as meaning a complex.

Claim 48 recites the limitation "viral antigen, tumor associated antigen and allergen" in reference to claim 32. There is insufficient antecedent basis for this limitation in the claim. Claim 32 recites that the stress protein is conjugated to an influenza antigen, so said antigen cannot be any other kind of antigen.

Claim 49 recites the limitation "viral antigen, tumor associated antigen and allergen" in reference to claim 32. There is insufficient antecedent basis for this limitation in the claim. Claim 32 recites that the stress protein is conjugated to an influenza antigen, so said antigen cannot be any other kind of antigen.

Claims 1-5, 13-41 and 43-49 are rejected under 35 U.S.C. §112, first paragraph, as the disclosure is enabling only for claims limited to the particular heat shock proteins hsp65 and hsp71 and conjugated to or in fusion with viral antigenic sequences..

Claims 1, 13, 18, 23, 28, 32, 36 and 40 are not limited to the specific stress proteins conjugated to or in fusion with the influenza antigens of the examples, but further extend to an ill-defined number of proteins. The application uses the word "homologous" indefinitely. The metes and bound of the term "homology" and "percent homology" are unclear. While Applicant can be their own lexicographer, a word cannot be used in a manner that is repugnant to one of ordinary skill in the art. One definition of a homolog, is something that has a common evolutionary origin with another. Sequence "homology" has also been used to quantify what is more appropriately termed sequence identity or sequence similarity (see Reeck and Lewin, attached). And even further, a homolog of a peptide could be a functional homolog wherein the same function of one peptide can be carried out by an unrelated peptide, or a structural homolog, wherein the secondary structures of two dissimilar peptides could be similar. The specification does not disclose methods of identifying polypeptides with a common evolutionary origin, nor does it address functional or structural homologs. As this word has a multitude of meanings, it renders the claims indefinite.

By convention, "homologous" implies an evolutionary relationship between proteins or genes which may or may not exist between the protein contemplated by Applicant. However, no discussion of an evolutionary relationship is presented in the disclosure. Presumably, Applicant intended for a protein sharing a certain "percent sequence identity" with the amino acid sequence of the stress protein of the specification. Yet, the specification lacks a written description of such a peptide (i.e., the amino acid sequence of the peptide is not disclosed) and it fails to teach how to make and identify such a peptide. For instance, the specification provides no clear definition of the amino acid sequences responsible for the functional characteristics of the peptides nor a teaching of how one identifies such sequences. More specifically, the specification does not teach what amino acids can be changed or substituted without substantially altering or destroying the biological activity of either the hsp protein or the influenza virus antigen. Further, it is well known in the art that sequence identity measures overall sequence similarity but does not teach the significance encoded by an amino acid substitution. Accordingly, it is not clear that a variant sequence which shares sequence identity to a specific peptide would have the functional characteristics in order to qualify as the specific peptide taught by the specification. Applicant describes various known types of stress proteins in the specification, but does not set forth what identifies these proteins as being suitable for use in the invention as it is now claimed. Each of these stress protein types have widely disparate functions in a cell, and would not necessarily be expected to provide the same immunoenhancing abilities of the stress proteins hsp65 and hsp71. Thus, variant sequences sharing sequence identity with the heat-shock proteins of the specification are not enabled by the specification. Accordingly, in view of the breadth of the

claims, the lack of guidance, the nature of the invention, and the lack of a working example, it would take an undue amount of experimentation for one of ordinary skill in the art to practice the invention commensurate in scope with the claims.

Claims 1-5, 13-41 and 43-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic compositions and methods of provoking an immune response, does not reasonably provide enablement for vaccine compositions and methods of preventing infection or disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification details the production of an in vitro CTL response to influenza antigens after immunization of mice with the claimed compositions. At no point is the specific CTL response of the mice shown to be protective from challenge virus. The specification does not set forth an accepted animal model experiment wherein challenge virus is administered after vaccination to illustrate a protective immune response. The protective immune response is the hallmark of a vaccine. The specification does not set forth any *in vitro* experiments detailing protective immune responses which could be extrapolated to *in vivo* situations, nor does it use an animal model which is accepted in the art for the study of influenza replication. As such, claims drawn to vaccine compositions or methods of preventing diseases caused by influenza are not enabled. Claims drawn to immunogenic compositions and methods of provoking specific CTL immune responses are enabled by the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 13-15, 17, 28-31, 41, 43, 44 and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by Roman et al. (Immunology 88(4): 487-492, August 1996).

The claims are drawn to vaccine or composition for inducing a CTL response comprising an influenza virus antigen such as hemagglutinin, nucleoprotein, neuraminidase, M1, M2, PB1, PB2, PA, that is either conjugated to or administered along with a stress protein such as hsp71 and hsp65.

Roman et al. teaches that synthetic peptides non-covalently bound to bacterial heat-shock protein 70 (Hsp70) elicit *in vivo* peptide-specific T-cell responses in the absence of adjuvant. Roman et al. teaches that hsp70 is an attractive candidate for specific vaccination against infectious diseases because hsp65 and hsp70 exert a strong helper activity *in vivo* when chemically conjugated to synthetic peptides. More specifically, Roman et al. discloses the construction of hsp70-pNP peptide complexes wherein the synthetic peptide is the influenza virus nucleoprotein (pNP) and the bacterial hsp70 is from *Mycobacterium tuberculosis* (see abstract). Roman et al. indicates that the influenza virus nucleoprotein was selected because it binds to *Mycobacterium tuberculosis* hsp70 and it is a good T-cell immunogen (page 487, 2nd col. 2nd ¶). Moreover, Roman et al. indicates that these complexes were highly effective for priming peptide-specific $CD4^+$ T-cell responses *in vivo* (page 487, 2nd col., 3rd ¶).

It appears that the hsp70 of the prior art is the same as the hsp71 of the claims. Furthermore, since the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the Applicant to prove that the claimed products are functionally different than those taught by the prior art and to

establish patentable differences. See Ex parte Phillips, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922, 1923 (PTO Bd. Pat. App. & Int.). Accordingly, Roman et al. anticipates the claimed invention.

Claims 1-4, 41 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Cohen (US Patent 5,736,146).

Cohen discloses hsp60 family stress proteins (hsp65) chemically conjugated to antigens such as viral, parasitic, or bacterial antigens. These complexes induce T cell reactivity to the antigen.

Claims 1-3, 13-17, 28-35, 41, 43, 44, 45, 47, and 48 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Srivastava (US Patent 5,837,251).

Srivastava discloses complexes of hsp proteins from the hsp60, hsp70 and hsp90 families in complex with antigens such as tumor antigens or influenza antigens. These complexes induce CD8+ CTL responses in vaccinated mice (columns 31 and 32). Claims 1 and 28 are representative claims. Srivastava specifically contemplates influenza antigens, for example, at column 24, section 5.4.

It appears that the hsp70 of the prior art is the same as the hsp71 of the claims. Furthermore, since the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the Applicant to

prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922, 1923 (PTO Bd. Pat. App. & Int.). Accordingly, Srivastava anticipates the claimed invention.

Claims 1-3, 13-17, 28-35, 41, 43, 44, 45, 47, and 48 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Srivastava (US Patent 5,935,576).

Srivastava discloses complexes of hsp proteins from the hsp60, hsp70 and hsp90 families in complex with antigens such as tumor antigens or influenza antigens. These complexes induce CD8+ CTL responses in vaccinated mice (columns 24 and 25). Claim 1 is a representative claim. Srivastava specifically contemplates influenza antigens, for example, at columns 18-19, section 5.6.

It appears that the hsp70 of the prior art is the same as the hsp71 of the claims. Furthermore, since the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the Applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray,

10 USPQ 2d 1922, 1923 (PTO Bd. Pat. App. & Int.). Accordingly, Srivastava anticipates the claimed invention.

Claims 1-3, 5, 41 and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by Suzue (PTO-1449 reference AR).

Suzue (Journal of Immunology 1996 vol 156 pages 873-879) discloses a fusion protein comprising HIV p24 in fusion with hsp70. This composition elicited both humoral and cellular responses. The fusion of the two proteins was determined to be necessary for proper immune stimulation.

It appears that the hsp70 of the prior art is the same as the hsp71 of the claims. Furthermore, since the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the Applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922, 1923 (PTO Bd. Pat. App. & Int.). Accordingly, Suzue anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roman et al. (Immunology 88(4): 487-492, August 1996) as applied to claims 1-3, 13-15, 17, 28-31, 41, 43, 44 and 47 above, in view of Cohen (US Patent 5,736,146).

Claims 18-22 recite that the hsp is conjugated to the influenza antigen.

Roman et al. teaches that synthetic peptides non-covalently bound to bacterial heat-shock protein 70 (Hsp70) elicit *in vivo* peptide-specific T-cell responses in the absence of adjuvant. Roman et al. teaches that hsp70 is an attractive candidate for specific vaccination against infectious diseases because hsp65 and hsp70 exert a strong helper activity *in vivo* when chemically conjugated to synthetic peptides. More specifically, Roman et al. discloses the construction of hsp70-pNP peptide complexes wherein the synthetic peptide is the influenza virus nucleoprotein (pNP) and the bacterial hsp70 is from *Mycobacterium tuberculosis* (see abstract). Roman et al. indicates that the influenza virus nucleoprotein was selected because it

binds to *Mycobacterium tuberculosis* hsp70 and it is a good T-cell immunogen (page 487, 2nd col. 2nd ¶). Moreover, Roman et al. indicates that these complexes were highly effective for priming peptide-specific $CD4^+$ T-cell responses *in vivo* (page 487, 2nd col., 3rd ¶). Roman et al. does not teach conjugation of the hsp to the influenza antigen.

Cohen discloses hsp60 family stress proteins (hsp65) chemically conjugated to antigens such as viral, parasitic, or bacterial antigens. These complexes induce T cell reactivity to the antigen. Cohen specifically contemplates the conjugation of viral antigens, as evidences by the claims drawn to compositions comprising HIV antigens.

Taken together, the instant invention appears to be the same or slightly different from the prior art of combining stress proteins and an antigen of interest. Roman discloses the benefits of combining influenza antigens and hsp70, and Cohen discloses that those antigens conjugated to one another provide good T cell reactivity upon immunization.

One of ordinary skill in the art at the time the invention was made would have been motivated to conjugate the influenza antigen to the stress protein so that the two moeities would be sure to stay together throughout the antigen presentation process, ensuring a better response. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 23-27, 36-40, 46 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roman et al. (Immunology 88(4): 487-492, August 1996) as applied to claims 1-3, 13-15, 17, 28-31, 41, 43, 44 and 47 above, in view of Suzue (Journal of Immunology 1996 vol 156 pages 873-879 PTO-1449 reference AR).

The claims state that the influenza antigen is in fusion with the stress protein.

Roman et al. teaches that synthetic peptides non-covalently bound to bacterial heat-shock protein 70 (Hsp70) elicit *in vivo* peptide-specific T-cell responses in the absence of adjuvant. Roman et al. teaches that hsp70 is an attractive candidate for specific vaccination against infectious diseases because hsp65 and hsp70 exert a strong helper activity *in vivo* when chemically conjugated to synthetic peptides. More specifically, Roman et al. discloses the construction of hsp70-pNP peptide complexes wherein the synthetic peptide is the influenza virus nucleoprotein (pNP) and the bacterial hsp70 is from *Mycobacterium tuberculosis* (see abstract). Roman et al. indicates that the influenza virus nucleoprotein was selected because it binds to *Mycobacterium tuberculosis* hsp70 and it is a good T-cell immunogen (page 487, 2nd col. 2nd ¶). Moreover, Roman et al. indicates that these complexes were highly effective for priming peptide-specific $CD4^+$ T-cell responses *in vivo* (page 487, 2nd col., 3rd ¶). Roman et al. does not teach fusion of the hsp to the influenza antigen.

Suzue (Journal of Immunology 1996 vol 156 pages 873-879) discloses a fusion protein comprising HIV p24 in fusion with hsp70. This composition elicited both humoral and cellular responses. The fusion of the two proteins was determined to be necessary for proper immune stimulation.

Taken together, the instant invention appears to be the same or slightly different from the prior art of combining stress proteins and an antigen of interest. Roman discloses the benefits of combining influenza antigens and hsp70, and Suzue discloses that those antigens in fusion with one another provide good T cell reactivity upon immunization. Suzue also indicates that a fusion between the moeities is necessary in order to induce the best immune response.

One of ordinary skill in the art at the time the invention was made would have been motivated to create a fusion protein comprising the influenza antigen in fusion with the stress protein so that the two moeities would be sure to stay together throughout the antigen presentation process, ensuring a better response. Suzue indicates this induces the strongest humoral and cellular immune responses. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner, can be reached on (703) 308-1032.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
September 29, 1999

DONNA WORTMAN
PRIMARY EXAMINER